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Award Number: W81XWH-04-1-0063

TITLE: Modeling Human Epithelial Ovarian Cancer in Mice by Alteration of Expression of the BRCA1 and/or p53 Genes

PRINCIPAL INVESTIGATOR: Denise C. Connolly, Ph.D.

CONTRACTING ORGANIZATION: Fox Chase Cancer Center
Philadelphia, PA 19111

REPORT DATE: February 2008

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
28-02-2008	Final	1 FEB 2004 - 31 JAN 2008

4. TITLE AND SUBTITLE
Modeling Human Epithelial Ovarian Cancer in Mice by Alteration of Expression of the BRCA1 and/or p53 Genes

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-04-1-0063

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Denise C. Connolly, Ph.D.

Email: dc_connolly@fccc.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Fox Chase Cancer Center
Philadelphia, PA 19111

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

About one out of every ten cases of epithelial ovarian cancer (EOC) is inherited. The majority, >90%, of inherited cases of EOC are the result of mutations in the breast cancer associated gene 1 {BRCAl). This gene was originally identified based on genetic linkage to families with an increased risk of developing breast and ovarian cancer. It is involved in controlling normal cellular growth and is thought to suppress the growth of tumors. That is, if BRCAl is mutated, the risk to develop breast and ovarian, cancer increases. Another gene that is important in the development of cancer is p53. It also helps maintain normal cellular growth and is the most commonly mutated gene in all human cancers. The p53 gene has been shown to be mutated in at least 50% of all cases of epithelial ovarian cancer. In addition to mutations of BRCAl, mutations of the p53 gene are often found in patients with breast and ovarian cancer syndrome. Based on the importance of both of these genes in the development of this type of ovarian cancer, we hypothesize that inactivation of BRCAl and p53 in the ovaries of mice will result in epithelial ovarian cancer in the animals.

15. SUBJECT TERMS
Ovarian Cancer, p53, BRCA1

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	10	USAMRMC

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

MODELING HUMAN EPITHELIAL OVARIAN CANCER IN MICE BY ALTERATION OF EXPRESSION OF THE *BRCA1* AND/OR *P53* GENES

PI: Denise C. Connolly
Final Progress Report, February 14, 2008

Introduction:

About one out of every ten cases of epithelial ovarian cancer is inherited. Unlike non-hereditary (sporadic) ovarian cancer, some of the underlying genetic causes of hereditary ovarian cancer are well understood. The majority, >90%, of inherited cases are the result of inherited mutations in the breast cancer associated gene 1 (*BRCA1*). This gene was originally identified based on genetic linkage to families with an increased risk of developing breast and ovarian cancer. It is involved in controlling normal cellular growth and is thought to suppress the growth of tumors. That is, if BRCA1 is mutated, the risk to develop breast and ovarian cancer increases. Another gene that is important in the development of cancer is the *p53* gene. It also helps maintain normal cellular growth and is the most commonly mutated gene in all human cancers. It has been shown to be mutated in at least 50% of all cases of epithelial ovarian cancer. In addition to mutations of *BRCA1*, mutations of the *p53* gene are often found in patients with breast and ovarian cancer syndrome. Based on the importance of both of these genes in the development of this type of ovarian cancer, we hypothesize that inactivation of *BRCA1* and *p53* in the ovaries of mice will result in epithelial ovarian cancer in the animals.

The objectives of this funded proposal are to:

1. develop mouse models of human epithelial ovarian cancer by inactivation of Brca1 and p53 singly or at the same time in the mouse ovarian surface epithelial cells;
2. investigate whether there is a difference between the complete absence of p53 or the presence of a dominantly acting p53 mutant in ovarian tumorigenesis in mice; and,
3. identify genes and cellular pathways, downstream of Brca1 and p53 inactivation/mutation, that contribute to ovarian carcinogenesis.

Body:

Specific tasks that were completed during the one year extension were 1) euthanasia and necropsy of remaining mice, 2) histopathological evaluation of tumor tissues, 2) verification of excision of conditional alleles in tumor tissue and 4) evaluation of genomic changes in a subset of tumors. All procedures described in this progress report involving animals were approved by Fox Chase Institutional Animal Care and Use Committee.

At the time of the 2007 progress report, a total of 161 mice had been euthanized and evaluated with 55 mice remaining alive on the study. Since then, the remaining 55 mice were euthanized and evaluated. Animals were euthanized if they exhibited palpable tumors or signs of illness or because they had reached old age without any symptoms of disease. In the absence of symptoms of disease, most animals were euthanized by the time they reached ~500 days in age. In rare cases animals that had expired overnight or over weekends were considered not suitable for tissue collection and further evaluation which accounts for small differences in the total numbers of mice injected versus the total number of mice evaluated. A summary of the total number of animals that were evaluated in each group is presented in Table 1. All animals were euthanized by CO_2 asphyxiation and were subjected to complete necropsy with gross pathological evaluation. All reproductive tract tissues and other affected tissues were removed and either fixed and processed for paraffin embedding and tissue sectioning or snap frozen in liquid nitrogen. Paraffin embedded tissue sections of reproductive tracts and all affected tissues were stained with hematoxylin and eosin (H&E) and evaluated

microscopically by the PI (D. Connolly) and by Dr. Lora Hedrick Ellenson, a board certified Gynecological Pathologist at Weill Cornell Medical College in New York. Paraffin embedded tissues of a number of tumors and affected tissues were also subject to immunohistochemical staining with antibodies to detect various cellular markers of differentiation (e.g., cytokeratin 8, cytokeratin 19, CD3, CD45 and α-smooth muscle actin) to assist in diagnosis of tumor histopathology. To confirm that tumor formation observed in mice is attributable to loss of *Brca1* and/or *p53* expression, tumor specimens were analyzed for excision of loxP flanked (floxed) sequences by PCR of genomic DNA isolated from tumor specimens. Genomic DNA from tumor specimens was isolated from snap frozen tumor specimens for large tumor specimens or by manual microdissection of neoplastic lesions identified in paraffin embedded and sectioned tissues. Over the course of the entire study, a total of 216 mice were euthanized and evaluated for tumor formation (**Table 1**). At the time of submission of this final progress report, all of the mice in Groups I-V have been evaluated.

Table 1. Summary of mice evaluated (including necropsy and histopathological evaluation of tissues).

	Group I	**Group II**	**Group III**	**Group IV**	**Group V**
Injection	**$Brca1^{LoxP/LoxP}$**	**$p53^{LoxP/LoxP}$**	**$Brca1^{LoxP/LoxP}$ $p53^{LoxP/LoxP}$**	**$Brca1^{LoxP/LoxP}$ $p53^{WT/R172H}$**	**$Brca1^{LoxP/LoxP}$ $p53^{LoxP/R172H}$**
Bilateral Ad5-CMV-Cre	**41**	**39**	**36**	**36**	**15**
Single ovary Ad5-CMV-Cre	**5**	**6**	**6**	**5**	**3**
PBS	**6**	**6**	**5**	**5**	**2**
Total number	**52**	**51**	**47**	**46**	**20**
Total = 216					

Of the 216 total mice evaluated, a number of neoplasms were observed and are summarized in **Table 2** (Ad5-CMV-Cre injected mice) and **Table 3** (PBS injected mice). Mice in **Group I** (*$Brca1^{LoxP/LoxP}$*) in which the *Brca1* gene was inactivated by Ad5-CMV-Cre injection developed neoplasms with a frequency of ~20% (9/42 mice). Only one ovarian neoplasm was identified and that was hilar cell tumor of the ovary. In one case (1/46 = 2.1%), we observed a vaginal squamous adenocarcinoma and two animals (2/46 = 4.3 %) had large masses over the front flank/shoulder that were identified as adenocarcinomas. Adenocarcinoma of the lung was observed in 4/46 (8.7 %) of the Ad5-Cre-CMV injected mice and in 1/6 (16.7 %) of the PBS control injected mice. The vaginal, shoulder and lung tumors in these mice were manually microdissected and subjected to genotyping analysis to confirm whether the floxed sequences present in the *Brca1* gene of these mice was excised. In none of these 7 cases were we able to demonstrate excision of the floxed sequences present in the *Brca1* gene were excised suggesting that these tumors are not related to loss of expression of *Brca1*. Tumors were observed in only three of 45 (6.6%) cases in **Group II** (*$p53^{LoxP/LoxP}$*) in which the *p53* gene was inactivated. Of these, two ovarian neoplasms were identified; one ovarian leiomyosarcoma (excision of both *Brca1* and *p53* alleles was confirmed by PCR amplification) and one ovarian hilar cell tumor. As predicted, the highest frequency of tumors observed to date were in the Ad5-CMV-Cre injected mice in **Group III** (*$Brca1^{LoxP/LoxP}$;$p53^{LoxP/LoxP}$*) in which both the *Brca1* and/or *p53* genes were inactivated. Tumors were observed in 52% (22/42) mice in this group. Ovarian tumors were observed in 26% (11/42) of these mice. Surprisingly, we did not observe epithelial ovarian tumors; rather, the ovarian tumors were poorly differentiated leiomyosarcoma of the ovary (**Figure 1**). Other tumors observed in this group were primarily (21%, 9/24 cases) poorly differentiated non-ovarian peritoneal sarcomas without distinct morphologic or immunohistochemical features. In **Group IV** (*$Brca1^{LoxP/LoxP}$;$p53^{WT/R172H}$*), in mice harboring homozygous floxed *Brca1*, one wild-type and one copy of a gain of function hot spot mutation *p53*, neoplasms were observed in 28% (10/36) mice, but none were ovarian tumors nor could excision of the *Brca1* allele be

demonstrated in any of these tumor tissues by PCR. Mice harboring a single copy of this mutant *p53* allele are known to develop spontaneous tumors with similar latency and histology as tumors that arise in $p53^{+/-}$ (1). We predicted that concomitant loss of expression of *Brca1* in the mouse ovary might result in epithelial ovarian cancers that outpaced these spontaneous tumors, but that does not seem to be the case in these mice. Based on these results we modified our experimental plan for **Group V** ($Brca1^{LoxP/LoxP};p53^{LoxP/R172H}$), and reduced the number of mice in this arm as it is expected that these mice would also be susceptible to spontaneous tumor formation related to the presence of the $p53^{R172H}$ allele. Accordingly, we reduced the number of mice in this arm by approximately half (Table 1) that of the other arms. Of the $Brca1^{LoxP/LoxP};p53^{LoxP/R172H}$ mice that received intrabursal injection of Ad5-CMV-Cre, 3/18 (16.6%) developed tumors. In one case of peritoneal sarcoma adjacent to the ovary was shown to have excision of the *Brca1* allele, whereas the one case of lymphoma there was no excision of the floxed sequences in *Brca1*.

Table 2. Summary of observed pathology in mice injected with Ad5-CMV-Cre. Number indicated is the percent and the numbers in parentheses are the number of mice with the indicated neoplasm out of the total number of mice in the group.

	Group I	Group II	Group III	Group IV	Group V
Ad5-CMv-Cre injected mice	**$Brca1^{LoxP/LoxP}$**	**$p53^{LoxP/LoxP}$**	**$Brca1^{LoxP/LoxP}$ $p53^{LoxP/LoxP}$**	**$Brca1^{LoxP/LoxP}$ $p53^{WT/R172H}$**	**$Brca1^{LoxP/LoxP}$ $p53^{LoxP/R172H}$**
Mice with tumors	**20 (9/46)**	**8 (3/39)**	**52 (22/42)**	**20 (8/41)***	**17 (3/18)**
Mice with ovarian tumors	**2 (1/46)**	**5 (2/39)**	**24 (11/42)**	**0 (0/41)**	**0 (0/18)**
Ovarian leiomyosarcoma	**0 (0/46)**	**3 (1/39)**	**17 (7/42)**	**0 (0/41)**	**0 (0/18)**
Uterine leiomyosarcoma	**0 (0/46)**	**0 (0/39)**	**2 (1/42)**	**0 (0/41)**	**0 (0/18)**
Uterine and ovarian leiomyosarcoma	**0 (0/46)**	**0 (0/39)**	**10 (4/42)**	**0 (0/41)**	**0 (0/18)**
Sarcoma	**0 (0/46)**	**0 (0/39)**	**21 (9/42)**	**10 (4/41)**	**6 (1/18)**
Tubal adenocarcinoma	**0 (0/46)**	**0 (0/39)**	**7 (3/42)**	**0 (0/41)**	**0 (0/18)**
Adenocarcinoma	**13 (6/46)***	**0 (0/39)**	**0 (0/42)**	**7 (3/41)**	**0 (0/18)**
Squamous carcinoma	**2 (1/46)***	**0 (0/39)**	**0 (0/42)**	**0 (0/41)**	**0 (0/18)**
Hilar cell tumor of ovary	**2 (1/46)**	**3 (1/39)**	**0 (0/42)**	**0 (0/41)**	**0 (0/18)**
Lymphoma	**0 (0/46)**	**3 (1/39)**	**0 (0/42)**	**5 (2/41)**	**6 (1/18)***
Unclassified tumor or necrotic mass	**2 (1/46)**	**0 (0/39)**	**5 (2/42)**	**0 (0/41)**	**6 (1/18)**

* No excision demonstrated

Table 3. Summary of observed pathology in PBS injected mice. Number indicated is the percent and the numbers in parentheses are the number of mice with the indicated neoplasm out of the total number of mice in the group.

	Group I	Group II	Group III	Group IV	Group V
PBS injected mice	**$Brca1^{LoxP/LoxP}$**	**$p53^{LoxP/LoxP}$**	**$Brca1^{LoxP/LoxP}$ $p53^{LoxP/LoxP}$**	**$Brca1^{LoxP/LoxP}$ $p53^{WT/R172H}$**	**$Brca1^{LoxP/LoxP}$ $p53^{LoxP/R172H}$**
Mice with tumors	**17 (1/6)**	**0 (0/6)**	**0 (0/5)**	**0 (0/5)**	**50 (1/2)**
Mice with ovarian tumors	**0 (0/6)**	**0 (0/6)**	**0 (0/5)**	**0 (0/5)**	**0 (0/2)**
Adenocarcinoma	**17 (1/6)**	**0 (0/6)**	**0 (0/5)**	**0 (0/5)**	**0 (0/2)**

Unclassified tumor or necrotic mass	**0 (0/6)**	**0 (0/6)**	**0 (0/5)**	**0 (0/5)**	**50 (1/2)**

All tumors were analyzed by microscopic evaluation of H&E stained tissue sections as well as tissue sections stained with various specific markers of cellular differentiation (e.g., cytokeratin 8, cytokeratin 19, CD3, CD45 and α-smooth muscle actin). Results from immunohistochemical analyses revealed no distinct or predictive staining patterns as many of the sarcomas were negative for these markers. Cases of tumors in which there was sufficient tissue were evaluated by PCR genotyping to confirm the presence or absence of floxed sequences of the *Brca1* and/or *p53* alleles. In **Group III**, the group with the highest incidence of tumor formation, most tumors were confirmed to have excision of both *Brca1* and *p53* alleles. However, in all other groups, excision was relatively infrequent suggesting that tumor formation was sporadic (e.g., in **Group I**, $BrcaA1^{LoxP/LoxP}$) or due to the presence of a gain of function mutant allele of p53 (e.g., **Group IV,** $Brca1^{LoxP/LoxP};p53^{WT/R172H}$ and **Group V** ($Brca1^{LoxP/LoxP};p53^{LoxP/R172H}$).

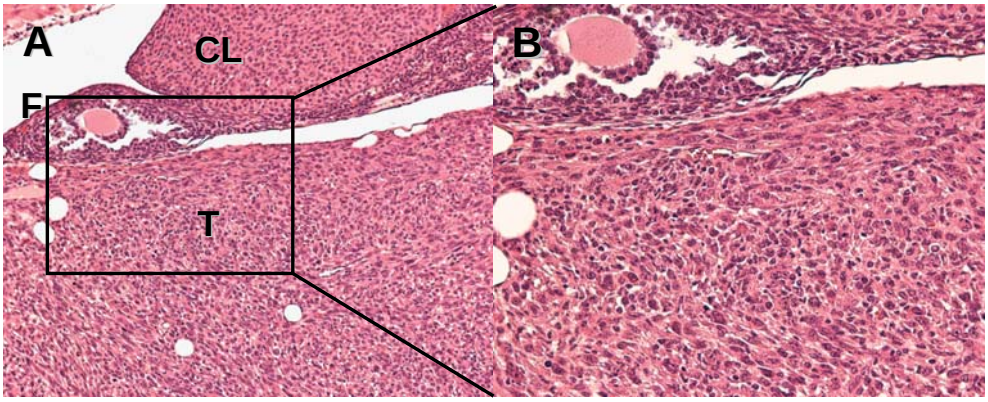

Figure 1. Ovarian leiomyosarcoma. Conditional inactivation of loxP flanked alleles of both *Brca1* and *p53* by intrabursal administration of Adenovirus-Cre results in ovarian leiomyosarcoma formation in ~24% of injected mice. Low power (10x) magnification (panel A) and 20x magnification (panel B) of an H&E stained section of an ovarian leiomyosarcoma isolated from a $BRCA1^{LoxP/LoxP};p53^{LoxP/LoxP}$ mouse 250 days after intrabursal injection with Adenovirus-Cre. F, follicle, T, tumor and CL, corpus luteum.

Ovarian sarcomas are rare (2) occurring in approximately 1-2% of *BRCA1* and *BRCA2* mutation carriers (3). In $Brca1^{LoxP/LoxP};p53^{LoxP/LoxP}$ mice which had the highest incidence, tumor formation occurred with relatively long latency (**Table 4**) suggesting that other genetic alterations contribute to tumorigenesis in this model. To test this hypothesis, we evaluated gross genomic alterations present in ovarian leiomyosarcomas by array comparative genomic hybridization (aCGH) and karyotyping of a leiomyosarcoma cell line derived from a tumor bearing mouse. These analyses revealed that ovarian sarcomas arising in $Brca1^{LoxP/LoxP};p53^{LoxP/LoxP}$ mice were accompanied by dramatic global genomic alterations as shown by both aCGH and karyotyping of the leiomyosarcoma cell line in **Figure 2**. The single ovarian sarcoma arising in the $p53^{LoxP/LoxP}$ group, while not normal, generally had patterns of whole chromosome gains and losses consistent with aneuploidy and many fewer regions of interstitial chromosomal gains/losses detected by aCGH as compared to tumors isolated from $Brca1^{LoxP/LoxP};p53^{LoxP/LoxP}$ mice (**Figure 2 A and C**). These results confirm previous studies showing that global genetic alterations are a common feature in *BRCA1* mutation carriers (4, 5).

Table 4. Average age in days at euthanasia (standard deviation).

	Group I	**Group II**	**Group III**	**Group IV**	**Group V**
Injection	**$Brca1^{LoxP/LoxP}$**	**$p53^{LoxP/LoxP}$**	**$Brca1^{LoxP/LoxP}$ $p53^{LoxP/LoxP}$**	**$Brca1^{LoxP/LoxP}$ $p53^{WT/R172H}$**	**$Brca1^{LoxP/LoxP}$ $p53^{LoxP/R172H}$**

Bilateral Ad5-CMV-Cre	**519 (105)**	**418 (45)**	**454 (107)**	**331 (110)**	**308 (76)**
Single ovary Ad5-CMV-Cre	**400 (88)**	**431 (5)**	**508 (75)**	**359 (88)**	**328 (8)**
PBS	**538 (56)**	**416 (22)**	**485 (50)**	**386 (85)**	**353 (10)**
OVERALL	**506 (112)**	**419 (40)**	**456 (112)**	**340 (106)**	**315 (67)**

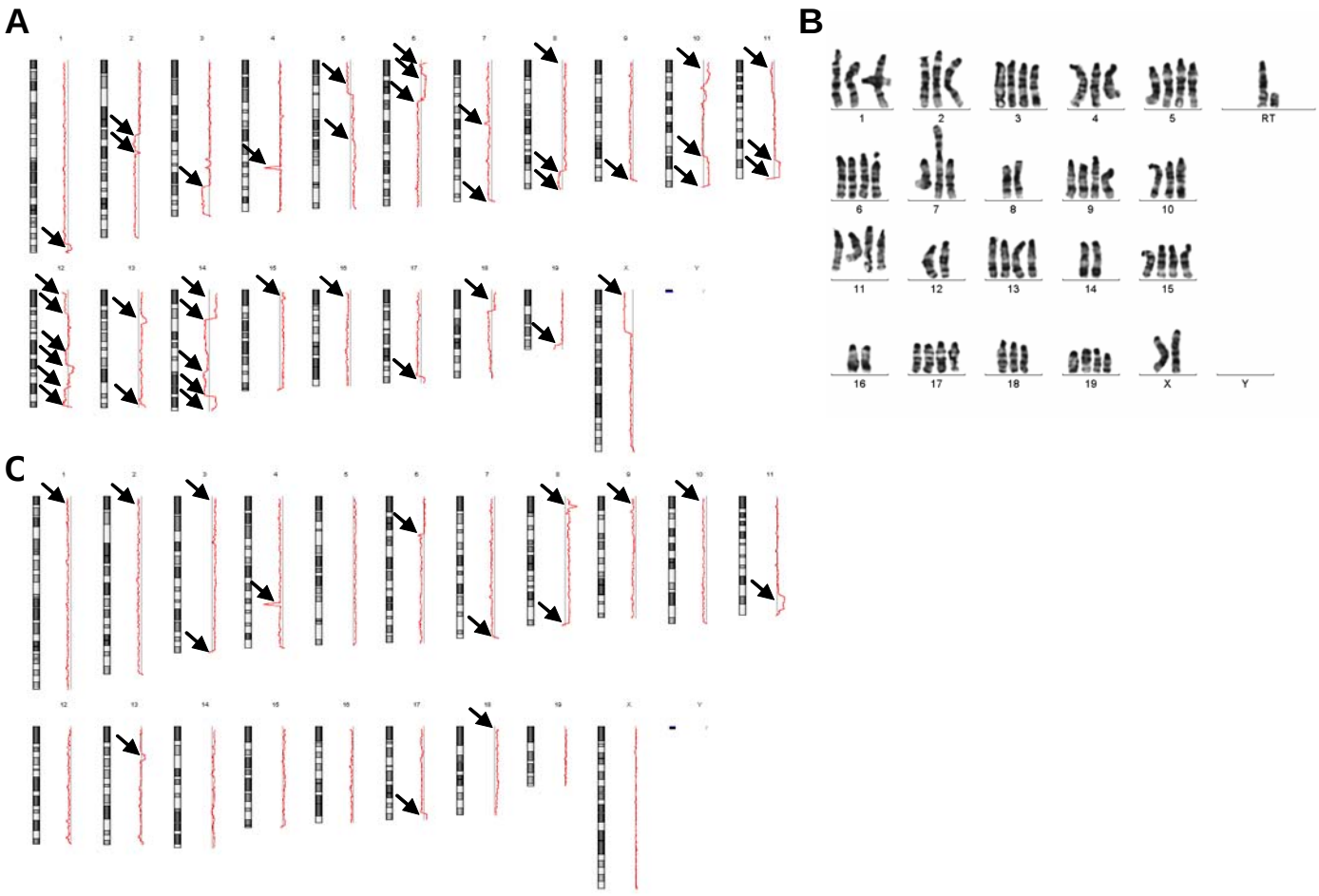

Figure 2. Array CGH and karyotyping analysis of ovarian sarcomas arising in *BRCA1$^{LoxP/LoxP}$;p53$^{LoxP/LoxP}$* and *p53$^{LoxP/LoxP}$* mice. Genomic DNA was isolated from an ovarian leiomyosarcoma and the corresponding tumor cell line isolated from *BRCA1$^{LoxP/LoxP}$;p53$^{LoxP/LoxP}$* mouse #399 and subjected to aCGH and karyotyping analysis (panels A and B). Numerous genomic alterations were identified (indicated by arrows on aCGH) including high level chromosome damage, variable chromosome counts, rearrangements and multiclonal populations (dicentrics, translocations, deletions, chromatid and chromosome breaks) are observed in this tumor. By comparison, genomic alterations in the tumor isolated from the *p53$^{LoxP/LoxP}$* mouse are fewer and consistent with gains/losses of entire chromosomes analogous with anueploidy.

Key Research Accomplishments:

- Completion of breeding of *Brca1$^{LoxP/LoxP}$/p53$^{LoxP/LoxP}$*, *Brca1$^{LoxP/LoxP}$/p53$^{R172H/WT}$* and *Brca1$^{LoxP/LoxP}$/p53$^{LoxP/R172H}$* mice required for the study

- Completion of intrabursal injections of 236 mice with either Ad5-CMV-Cre or PBS (56 *Brca1*$^{LoxP/LoxP}$, 53 *p53*$^{LoxP/LoxP}$, 54 *Brca1*$^{LoxP/LoxP}$/*p53*$^{LoxP/LoxP}$, 53 *Brca1*$^{LoxP/LoxP}$/*p53*$^{R172H/WT}$ and 20 *Brca1*$^{LoxP/LoxP}$/*p53*$^{LoxP/R172H}$ mice)
- Euthanasia, complete necropsy and tissue collection on 216 mice
- Histopathological evaluation of tissue specimens from these 216 mice
- PCR analysis of genotype and gene excision of tumor tissues
- Immunohistological staining of tumor specimens for expression of cellular markers of differentiation including cytokeratin 8, cytokeratin 19, CD3, CD45, α-smooth muscle actin (α-SMA)
- Established tumor cell line from a *Brca1*$^{LoxP/LoxP}$/*p53*$^{LoxP/LoxP}$ ovarian leiomyosarcoma
- Array CGH and karyotyping analysis of selected tumors and leiomyosarcoma cell line

Reportable Outcomes:

- Conditional inactivation of *loxP* flanked alleles of either *Brca1* or *p53* alone by intrabursal injection of Adenovirus-Cre recombinase rarely results in tumor formation
- Conditional inactivation of *loxP* flanked alleles of both *Brca1* and *p53* genes in the mouse ovary by intrabursal injection of Adenovirus-Cre recombinase results in a high frequency of ovarian and non-ovarian neoplasms
- Frequency and latency of tumor formation
- Tumor histology
- Tumors arising in mice with conditional inactivation of both *Brca1* and *p53* genes are accompanied by global genomic instability
- Tumors arising in mice with conditional activation of the *p53* gene are accompanied by genomic alterations consistent with aneuploidy

Conclusions:

Inactivation of conditionally expressed *loxP* flanked alleles of the *Brca1* and/or *p53* genes in the mouse ovary by intrabursal injection of Adenovirus-Cre recombinase results in a high frequency of ovarian and non-ovarian neoplasms. Unlike a previously reported mouse model of epithelial ovarian cancer resulting from conditional inactivation of the *p53* and *Rb* genes in the mouse ovary (6), the incidence of epithelial ovarian carcinomas is rare in mice with conditional inactivation of both the *Brca1* and *p53* genes. We have communicated our results with our colleagues at meetings and have learned that other groups performing similar experiments have had similar results. Although this is not the predicted outcome, the results of this study are reportable. A manuscript (Quinn, et al, in preparation) reporting these results is in the final stages of preparation and will be submitted for publication within the next 4-6 weeks.

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Publications:

1. Quinn, B.A., Brake, T., Hua, X., Baxter-Jones, K.A., Ellenson, L.H. and Connolly, D.C. Conditional inactivation of *Brca1* and *p53* results in ovarian tumor formation in mice. Manuscript in preparation.

List of Personnel:

Denise C. Connolly, Ph.D. – Assistant Member
Tiffany Brake, Ph.D. – Postdoctoral Associate
Kimberly A. Baxter-Jones, B.S. – Scientific Technician I
Thuy Tran – Summer Assistant II
Bridget A. Quinn, B.S. – Scientific Technician
Jennifer Zellers – Summer Assistant
Nika Priest, B.A., M.M.S. – Scientific Technician II

Appendices:

None